

Current Treatment Approaches for HIV-infected Pregnant Women: Progress and Challenges

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Elective cesarean section and combination antiretroviral therapy are new approaches for treating HIV-infected pregnant women. However, the morbidity associated with cesarean section, the side effects of antiretrovirals, and the provision of effective long-term contraception for women who are not planning another pregnancy present ongoing challenges.

Progress

A breakthrough study by the European Mode of Delivery Collaboration ("European randomized mode of delivery trial: elective cesarean at 38 weeks vs. vaginal delivery." *Lancet* 1999;353:1035-9) indicated a significantly lower transmission rate ((1.8%, N=170) in those HIV-infected pregnant women undergoing elective cesarean section compared with those (10.5%, N=200) who delivered vaginally. Not all patients in the study received antiretroviral therapy.

The International Perinatal HIV Group did a meta-analysis of 15 prospective cohort studies on mode of delivery and the risk of vertical transmission of human immunodeficiency virus (*New England Journal of Medicine* 1999 Apr 1;340(13):977-87). The meta-analysis revealed a 50% reduction in transmission in women undergoing cesarean sections (antiretroviral treatment of women in these studies was unknown). Women receiving antiretroviral therapy and undergoing cesarean sections showed an 87% reduction in transmission (2%–7% transmission rate).

This meta-analysis resulted in the following ACOG Committee Opinion (Number 219, August 1999):

- All HIV-infected women should be offered scheduled cesarean section at 38 weeks.
- Woman's choice whether to deliver by cesarean section must be respected.
- Combination drug regimen may reduce the risk of transmission to such low levels that cesarean section may not offer additional benefit.

There are several potent regimens of combination antiretroviral therapy (two nucleoside analog reverse transcriptase inhibitors plus a potent, bioavailable protease inhibitor). However, except for zidovudine, we do not have much information on the toxicity of these agents. Many effectively treated persons will demonstrate a rapid rate of decline in plasma HIV RNA concentrations and then a more gradual phase of decline to below detectable levels by approximately 8 weeks after initiation of combination therapy (*MMWR* 1998;47[No. RR-5]).

Recent studies (Garcia PM, et al. *New England Journal of Medicine* 1999 Aug 5;341(6):394-402; Mofenson LM, et al. *New England Journal of Medicine* 1999 Aug 5;341(6):385-93; and Clarke SM, et al. *International Journal of STD & AIDS* 2000 Apr;11(4):220-3) have examined the relationships between viral load, combination therapy, and the vertical transmission of HIV. Some of the findings were:

- There does not appear to be threshold below which lack of transmission can be assured.

- Rate of transmission in women with undetectable viral loads was similar to those who receive ZDV and undergo elective cesarean section.
- Transmission occurred in 1 of 364 women with viral load less than 500 copies per mL.
- Transmission occurred in 6 of 461 women who received 2 or more antiretrovirals.

Challenges

There seems to be increased morbidity associated with cesarean section vs. vaginal delivery. JS Stringer, et al. (*JAMA* 1999 May 26;281(20):1946-9) suggest there is cause for restraint when considering elective cesarean section:

- Associated with protective effect in some observational studies but not others.
- In the independent meta-analysis previously cited, approximately 62% of mothers did not receive antiretroviral therapy.
- Results from meta-analysis cannot substitute for a randomized controlled trial (RCT).
- Meta-analysis of even RCT will predict an effect that will later be discredited by large randomized trials as often as 35% of the time.

The European RCT of mode of delivery in HIV-infected pregnant women (previously cited) did not find any major morbidity in the study or control population, but fever was more likely in those undergoing cesarean section (6.7% vs. 1.1%). DH Watts, et al. (*American Journal of Obstetrics & Gynecology* 2000 Jul;183(1):100-7) reported that: “Endometritis and wound infection occurred more frequently among human immunodeficiency virus–infected women after cesarean than among women undergoing vaginal delivery; however, complication rates overall were within the range reported in human immunodeficiency virus–negative women.” In addition: “Any peripartum infection occurred among 16 (18%) of those with a CD4 count of $<200/\mu\text{L}$ and 43 (13%) with a CD4 count of $\geq 200/\mu\text{L}$ ($P = .17$).”

The safety of antiretrovirals for pregnant women must also be considered. In 13 monkeys exposed to the frequently used drug efavirenz (sustiva), 3 had offspring with birth defects (1 cleft palate, 1 microphthalmia, and 1 anencephaly). In 1998 the FDA issued an alert indicating that sustiva should not be used in pregnant women.

Since Dr. Mofenson has already discussed the potential mitochondrial toxicity of antiretrovirals, I will skip this topic.

On January 5, 2001, Bristol Myers Squibb issued the following caution on the combination of stavudine and didanosine:

- 3 cases of fetal lactic acidosis have been reported:
2 pregnant: one antepartum and one postpartum
- 2 infants died: intrauterine fetal death at 32 weeks, and neonatal death at 36 weeks, after emergent cesarean section
- several nonfatal cases of pancreatitis with or without lactic acidosis or hepatic failure in pregnant women have been reported
- the combination should be used with caution during pregnancy; recommended only if benefit outweighs risk.

About 60% of women who have a repeat pregnancy report that the pregnancy was not planned. Thus

long-term contraception for women who are not planning another pregnancy remains an important challenge. Potential methods of postpartum conception that should be considered include: condoms, Depo-Provera, Norplant, tubal ligation, oral contraceptive pill, barrier method, morning-after pill, and natural family planning.

In summary, potential prevention strategies for risk factors for perinatal HIV transmission are (modified from *Clinical Obstetrics and Gynecology* 1996;39:386-95):

**Risk Factors for Perinatal HIV Transmission
and Potential Prevention Strategy**

<u>Risk Factor</u>	<u>Prevention Strategy</u>
Maternal disease status	Antiretroviral therapy
Obstetrical determinants	Elective cesarean section Avoid rupture of membranes Avoid invasive procedure

Finally, insure that all HIV-infected pregnant women receive long-term therapy and follow-up.